

## REMARKS

### 1. Preliminary Remarks

#### a. Status of the Claims

Claims 150-177 and 179-196 are pending in this application, of which claims 179-196 are under active consideration. Claim 195 is amended. Applicant respectfully requests entry of the remarks and amendments made herein into the file history of the application. Upon entry of the amendments, claims 150-177 and 179-196 will be pending, and claims 179-196 will be under active consideration.

#### b. Claim Amendments

Claim 195 is amended to correct a typographical error.

#### c. Claim Objections

On page 2 of the Office Action, the Examiner objects to claim 195 over the phrase, “replicationdeficient.” Amended claim 195 corrects this typographical error to, “replication deficient,” thereby obviating the objection.

### 2. Patentability Remarks

#### a. 35 U.S.C. § 102

On pages 3 and 4 of the Office Action, the Examiner rejects claims 179, 181, 183, 187, and 195 under 35 U.S.C. § 102(b) as allegedly being anticipated by Steegenga *et al.* (Oncogene, 1998;16:349-57) (“Steegenga I”). Applicant respectfully disagrees, since the Examiner has failed to provide evidence that Steegenga I teaches all of the limitations of the instant claims.<sup>1</sup> In particular, the Examiner has not shown that the cited reference discloses a recombinant adenovirus that expresses E1B, E4, or E1B and E4 before it expresses E1A.

The instant claims relate to a recombinant adenovirus, “wherein upon infection... the adenovirus expresses a first polypeptide comprising an E1B polypeptide, an E4 polypeptide or an E1B and E4 polypeptide prior to expressing a second polypeptide comprising an E1A polypeptide.”<sup>2</sup> Accordingly, the claimed adenovirus expresses E1A after it expresses E1B, E4, or

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<sup>1</sup> See MPEP § 2131 *quoting* *Verdegaal Bros. v. Union Oil Co. of Calif.*, 814 F.2d 628, 631 (Fed. Cir. 1987) (“A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference”).

<sup>2</sup> Instant claim 179.

E1B and E4. This order is the opposite to that of a wild-type adenovirus, as disclosed by the instant specification.<sup>3</sup>

In stark contrast to the instant claims, the Examiner has failed to establish that Steegenga I discloses an adenovirus that expresses E1A and E1B or E4 in the opposite order to wild-type. The Examiner points to Figure 6 of Steegenga I, but this figure does not even disclose an adenovirus,<sup>4</sup> while an adenovirus is a key component of the instant claims. Instead, Figure 6 only discloses E1B and E4 co-expression using the same type of pCMV expression vector.<sup>5</sup> Furthermore, this figure includes no description of E1A expression. Not only does Figure 6 fail to disclose an adenovirus, or any E1A protein expression, but the Examiner has also failed to provide any explanation as to how this figure reveals a reversed order of expression for E1A and E1B or E4. Absent any additional evidence, no inference can be drawn about the order of expression of E1A as compared to E1B and E4, and it would be unreasonable to conclude that the expression order is opposite to wild-type. Rather, based on the teachings of Steegenga I, one of skill would reasonably conclude that E1A expression naturally precedes E4 expression, since Steegenga I discloses, “previously reported stimulation of E4orf6 expression by the E1A proteins.”<sup>6</sup> Again, this order of expression is the opposite from that of the claimed adenovirus, as disclosed in the instant application. Accordingly, the Examiner has failed to establish that Steegenga I discloses all of the limitations of the instant claims, and the claims are therefore not anticipated by Steegenga I. In view of the foregoing, Applicant respectfully requests that the Examiner reconsider and withdraw the rejection of claims 179, 181, 183, 187, and 195 under 35 U.S.C. § 102.

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<sup>3</sup> See Instant Specification at page 15, line 4 (“The present invention is based on the surprising finding that the reversal of the expression sequence of adenoviral genes results in an efficient replication and optionally in the lysis of the cell infected by the adenovirus. With regard to the chronologically changed expression of the adenoviral genes, particular emphasis is to be put on an E1B protein and an E4 protein which are also referred to herein... as the first protein, which are expressed prior to the second protein. The second protein is selected from the group comprising [sic] E1A protein. **This expression sequence which is reversed compared to the wildtype adenoviruses...**”) (emphasis added).

<sup>4</sup> See Steegenga I at Figure 6 (disclosing transient transfection of pCMV expression vectors containing E1B or E4orf6) and see also Steegenga I at page 356, column 2, line 42 (“Hep3B were transiently transfected by way of the calcium-phosphate precipitation method... 0.1 µg pCMV-p53 was cotransfected with pCMV-55k [a form of E1B] and/or pCMV34K [the E4orf6 form of E4] as indicated in Figure 6”).

<sup>5</sup> See Steegenga I at Figure 6 (“The large E1B and E4orf6 proteins together can down-regulated p53... p53-negative Hep3B cells were... cotransfected with either pCMVnco, pCMV-E1B, pCMV-E4orf6 or combinations of these plasmids...”).

<sup>6</sup> Steegenga at page 353, column 2, line 38.

**b. 35 U.S.C. § 103****(1) Claims 179, 180, 181, 183, 187, and 195 over Steegenga I in view of Fueyo**

On pages 4-7 of the Office Action, the Examiner rejects claims 179, 180, 181, 183, 187, and 195 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Steegenga I in view of U.S. Patent Application Publication No. 2005/0260162 ("Fueyo"). Fueyo is cited as allegedly disclosing an E1B55 Kd polypeptide, and the Examiner otherwise relies on the characterization of Steegenga I above. The Examiner concludes that it would have been obvious for one of ordinary skill in the art to combine the teachings of Steegenga I and Fueyo to arrive at the claimed subject matter. Applicant respectfully disagrees, because the Examiner has failed to make a *prima facie* case of obviousness.

In particular, the Examiner has not properly ascertained the differences between the claimed invention and the prior art, as required under the analysis set forth by *Graham v. John Deere Co.*, 383 U.S. 1 (1966).<sup>7,8,9</sup> As a result, the Examiner has failed to explain how the combined teachings of Steegenga I and Fueyo teach all of the limitations of the instant claims, or obviate the claimed subject matter, and thus has not made a *prima facie* case of obviousness.<sup>10</sup> In particular, the Examiner offers no explanation as to why it would have been obvious, in light of the teachings of Steegenga I and Fueyo, for one of ordinary skill in the art to arrive at the claimed adenovirus, which expresses E1A and E1B or E4 in an order opposite to wild-type. This limitation is clearly required by the instant claims.<sup>11</sup> Since the Examiner has failed to meet the burden of establishing a *prima facie* case, Applicant submits that the claimed subject matter is not obvious over the cited art. In view of the foregoing, Applicant respectfully requests that the Examiner reconsider and withdraw the rejection

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<sup>7</sup> See MPEP § 2141.II citing *Graham*, 383 U.S. 1 ("Obviousness is a question of law based on underlying factual inquiries. The factual inquiries enunciated by the Court are as follows ... (B) Ascertaining the differences between the claimed invention and the prior art.... The question of obviousness must be resolved on the basis of these factual determinations") (emphasis added).

<sup>8</sup> Fueyo even discloses adenoviruses where the nucleic acid encoding E1B 55Kd is deleted, so that it would be impossible for this virus to express E1B before E1A.

<sup>9</sup> Fueyo also fails to overcome the lack of description in Figure 6 of Steegenga I regarding the order of E1A and E1B or E4 expression.

<sup>10</sup> See MPEP § 2141.III citing *Dann v. Johnston*, 425 U.S. 219 (1976) ("The prior art reference (or references when combined) need not teach or suggest all the claim limitations, however, Office personnel must explain why the difference(s) between the prior art and the claimed invention would have been obvious to one of ordinary skill in the art") (emphasis added).

<sup>11</sup> Instant claim 179, *supra*.

of claims 179, 180, 181, 183, 187, and 195 under 35 U.S.C. § 103(a) over Steegenga I in view of Fueyo.

**(2) Claims 179, 181-183, 187, and 195 over Steegenga I in view of Steegenga II**

On pages 7-9 of the Office Action, the Examiner rejects claims 179, 181-183, 187, and 195 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Steegenga I in view of Steegenga (Molecular and Cell Biology, 1999;19(5):3885-98) ("Steegenga II"). Steegenga II is cited as allegedly disclosing an E1A12S polypeptide, and the Examiner otherwise relies on the characterization of Steegenga I above. The Examiner concludes it would have been obvious for one of ordinary skill in the art to combine the teachings of Steegenga I and Steegenga II to arrive at the claimed subject matter. Applicant respectfully disagrees, for the same reasons discussed above.

Namely, the Examiner has failed to make a *prima facie* case of obviousness since the Examiner has not given any explanation as to why it would have been obvious in light of the teachings of Steegenga I and Steegenga II for one of ordinary skill in the art to arrive at an adenovirus that expresses E1A and E1B or E4 in an order opposite to wild-type. In particular, the teachings in Steegenga II on the effects of E1A12S on p53 and p73 (which are purported to be similar), and the effects of E1B and E4 on p53 and p73 (which are purportedly different), have no bearing on the instantly claimed order of E1A and E1B or E4 expression. In view of the Examiner having failed to make a *prima facie* case of obviousness, Applicant submits that the claimed subject matter is not obvious over Steegenga I and Steegenga II. In view of the foregoing, Applicant respectfully requests that the Examiner reconsider and withdraw the rejection of claims 179, 181-183, 187, and 195 under 35 U.S.C. § 103(a) over Steegenga I in view of Steegenga II.

**(3) Claims 179 and 181-196 over Steegenga I in view of Steegenga II, Irving, and Li**

On pages 9-14 of the Office Action, the Examiner rejects claims 179 and 181-196 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Steegenga I in view of Steegenga II, and further in view of U.S. Patent Application Publication No. 2003/0095989 ("Irving") and Li *et al.* (Cancer Research, 2001;61:6428-36) ("Li"). Irving is cited as allegedly disclosing a first or second polynucleotide operably linked to a YB-1-controlled promoter, Li is cited as allegedly disclosing an IRES sequence that separates nucleic acids sequences encoding first and second polypeptides, and the Examiner otherwise relies on the characterization of Steegenga I above. The Examiner concludes that it would have been obvious for one of ordinary skill in the art to combine the

teachings of Steegenga I, Steegenga II, Irving, and Li to arrive at the instantly claimed subject matter. Applicant respectfully disagrees, for the same reasons discussed above.

Namely, the Examiner has failed to make a *prima facie* case of obviousness since the Examiner has not given any explanation as to why it would have been obvious in light of the teachings of Steegenga I, Steegenga II, Irving, and Li for one of ordinary skill in the art to arrive at an adenovirus that expresses E1A and E1B or E4 in an order opposite to wild-type. In view of the Examiner having failed to make a *prima facie* case of obviousness, Applicant submits that the claimed subject matter is not obvious over Steegenga I, Steegenga II, Irving, and Li. In view of the foregoing, Applicant respectfully requests that the Examiner reconsider and withdraw the rejection of claims 179 and 181-196 under 35 U.S.C. § 103(a) over Steegenga I in view of Steegenga II, Irving, and Li.

**c. Obviousness Type Double Patenting**

On pages 14 and 15 of the Office Action, the Examiner provisionally rejects claims 179-185, 187-191, and 194-196 on the ground of nonstatutory obviousness-type double patenting as allegedly being unpatentable over claims 47-51, 53, 59, 60, and 65 of copending U.S. Patent Application No. 10/451,210 (the “’210 Application”). Applicant respectfully requests that the Examiner hold the rejection over the ’210 Application in abeyance until there is allowable subject matter, at which time the Applicant will consider amending the claims in the ’210 Application, or filing a terminal disclaimer.

### 3. Conclusion

Applicant respectfully submits that the instant application is in good and proper order for allowance and early notification to this effect is solicited. If, in the opinion of the Examiner, a telephone conference would expedite the prosecution of the instant application, the Examiner is encouraged to call the undersigned at the number listed below.

Respectfully submitted,

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